International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol. 24 No. 12 – 1986 (pp. 646–650)

Suanzaorentang versus diazepam: a controlled double-blind study in anxiety

H. C. CHEN[1], M. T. HSIEH[1] and T. K. SHIBUYA[1, 2]

[1]*Institute of Chinese Pharmaceutical Sciences, China Medical College and Hospital, Taichung 400, Taiwan, ROC*
[2]*Department of Pharmacology, Tokyo Medical College, Shinjuku, Tokyo 160, Japan*

Abstract. The ancient Chinese remedy Suanzaorentang was originally described in Kin-Kue-Yao-Lueh for patients with weakness, irritability and insomnia. In our preliminary observations on suanzaorentang, it seemed to be a promising anxiolytic remedy. A controlled comparative double-blind clinical trial was set up to assess the anxiolytic effect of suanzaorentang. Suanzaorentang (250 mg t.i.d.) and diazepam (2 mg t.i.d.) had almost the same anxiolytic effect. However, suanzaorentang, but not diazepam, improved the psychomotor performance during the daytime. No significant subjective side effects were observed during treatment with suanzaorentang. All laboratory tests, including liver function tests (serum SGOT, SGPT, albumin, globulin, bilirubin), renal function tests (BUN, serum creatinine), electrolyte balances (serum K^+, Na^+, Cl^-, Ca^{++}), serum cholesterol-triglyceride-HDL-c, thyroid function test (serum T_4), chest P-A X-ray film, blood-urine-stool routine examinations (BUS routines), were unaltered after one week's administration of the compound.

Key words: suanzaorentang – diazepam – anxiety

Introduction

Anxiety is a state of excessive fear. It may be diagnosed on the basis of 3 of the following 4 symptoms: motor tension, sympathetic hyperactivity, apprehension and vigilance [American Psychiatric Association 1980]. Anxiety may interfere with intelligence [Wittenborn et al. 1979] and psychomotor function [Lader 1979]. Diazepam is the most frequently prescribed anxiolytic agent in Taiwan. Although diazepam improves the anxious mood and accompanying symptoms, it may dull the needed alertness. It was found that the road traffic accident victims were much more likely to have taken diazepam than the control group [Bo et al. 1974]. Searching for "ataractics" in China may be traced back to about 2000 years ago when the formula of suanzaorentang was described in the medical book called Kin-Kue-Yao-Lueh (Chang 115 B.C.). Modern Chinese physicians still use it for sedation.

In our previous observations of this formula [Chen and Hsieh 1985], we found that it was a promising anxiolytic remedy. There are five components in suanzaorentang: zizyphi semen, poria, ligustici chuanxiong rhizoma, anemarrhenae rhizoma and glycyrrhizae radix. We have tested different combinations and preparations of the components in rats to get the most sedative effects. The only two components showing any sedative effects were zizyphi semen and ligustici chuanxiong rhizoma; however, these effects were not nearly as strong as that of suanzaorentang. A modified suanzaorentang compound was specifically prepared by the Institute of Chinese Pharmaceutical Sciences and then a controlled comparative double-blind study was set up to evaluate it. The study design of the present clinical trial is essentially the same as that of Salkind's (1979). The reasons for the design may be referred to the original paper.

Reprint requests to Dr. H. C. Chen.

Materials and methods

Preparation of suanzaorentang

The preparation consisted of coarse powders of zizyphus spiuosus hu (rhumnaceae), poria cocos (Schw.) Wolf (polyporaceae), ligusticum chanxiong Hort (umbelliferae), anemarrhena asphodeloides Bunge (liliaceae) and glycyrrhiza uralensis Fischer et DC (leguminosae) (Min Tong Pharmaceutical Co., LTD.), in the ratio of 7.5 : 2 : 2 : 1 : 1.

The mixture (1 kg) was immersed in 5000 ml of 95% alcohol at room temperature for three days and then extracted in water bath

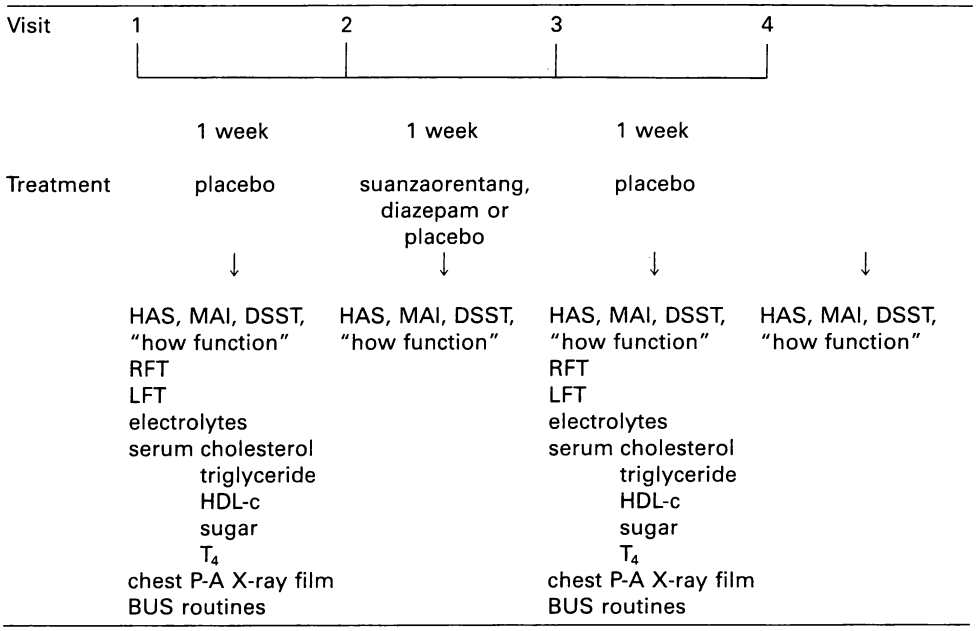

Fig. 1 Study plan. (HAS: Hamilton Anxiety Scale, MAI: Morbid Anxiety Inventory, DSST: Digital Symbol Substitution Test, "how function": how well do you function during the daytime, RFT: renal function tests, LFT: liver function tests, BUS routines: blood-stool routines examinations).

at a temperature below 80° C several times until the solution was clear. The extracted solution was evaporated and concentrated in a rotary vacuum evaporator at a temperature below 60° C. The sample was obtained by lyophilizing the concentrated extract and then pulverizing it through a No. 80# mesh. Finally, the powder was poured into capsules (250 mg/capsule).

Patients

Patients with anxiety and a Morbid Anxiety Inventory (MAI) score between 14 and 30 [Salkind et al. 1979] were selected as potential subjects for the study. The following patients were excluded in the present studies: patients with other specific conditions (e.g. hypertension, hepatitis, angina pectoris), patients who had taken any medication in the preceeding 4 weeks and pregnant women.

From an anxiety special clinic, the sample was drawn by the presenting sampling technique.

The rating of anxiety and psychomotor performance

Anxiety was rated by the MAI [Salkind 1973] and the Hamilton Anxiety Scale (HAS) [Hamilton 1959]. Psychomotor performance was rated by a Digital Symbol Substitution Test (DSST) [Wechsler 1955]. A clinical global rating of "how well do you function during the daytime?" ("how function") scale was made. In the "how function" scale, a 5 point scale relating to the subject's usual state prior to entering the study (1 much worse, 2 worse, 3 variable or moderate improvement, 4 good improvement and 5 dramatic improvement) was used.

At around 9 am, the ratings were made in a psychometric laboratory with the help of a well-trained technician who was blind to the mediation being taken.

Study plan

As shown in Figure 1, all patients were initially given placebo. After 1 week, patients were re-assessed and those who still scored 14 or more on the MAI were admitted to the controlled comparative double-blind part of the trial for 1 week. Patients entering the 2nd phase of the clinical trial were randomly assigned to 1 of the 3 treatment groups: diazepam 2 mg t.i.d., suanzaorentang 250 mg t.i.d. and placebo. Diazepam, suanzaorentang and placebo were made indistinguishable in appearance. After the 2nd week, placebo was prescribed again for 1 week. Patients started on a dose of three capsules a day but were allowed to take up to a maximum of 6 capsules a day or to decrease the doses if possible. Patients were dispersed 42 capsules to last the 7 days between visits and capsules not taken were returned and counted. The rating of anxiety and psychomotor performance were made at visit 1, 2, 3 and 4. Any significant life events and subjective adverse effects were enquired about.

At visit 1 and 3, the following tests were made to rule out any other specific conditions and to estimate the adverse effects: renal function test (RFT: BUN, serum creatinine), liver function tests (LFT: serum SGOT, SGPT, albumin, globulin, bilirubin), electrolyte balances (serum K^+, Na^+, Cl^-, Ca^{++}), serum cholesterol-triglyceride-HDL-c, fasting blood sugar, serum T_4, chest P-A X-ray film, blood-urine-stool routine examinations (BUS routines).

Statistical analysis

The unpaired Student's t-test was applied to comparisons between two separate groups of persons and paired Student's t-test was applied to comparisons between two occasions in the same persons. A p value $\leqq 0.05$ by two-tailed analysis was required for statistical significance.

Table 1 Characteristics of the subjects completing study.

	suanzaorentang	diazepam	placebo
Number of subjects	32	28	30
Age (years)	36 ± 9	33 ± 8	35 ± 9
Sex (male/female)	15/17	16/12	14/16
MAI score before treatment	26.4 ± 7.6	28.9 ± 8.2	27.4 ± 8.1
HAS score before treatment	24.2 ± 5.9	23.6 ± 6.2	24.5 ± 6.0

Mean ± SD

Table 2 Capsule count during the 2nd week (Mean ± SD).

Treatment	Total number of capsules taken	Average number of capsules taken per day
Suanzaorentang (250 mg/capsule)	22 ± 11	3.1 ± 1.6
Diazepam (2 mg/capsule)	25 ± 12	3.6 ± 1.7
Placebo	33 ± 10	4.7 ± 1.5

Results

Patients

Totally, 99 patients entered the study, 9 dropped out for various reasons including unwillingness to fill out forms (2 in the placebo group, 1 in the diazepam group, 1 in the suanzaorentang group), significant life events due to myocardial infarction and traffic accident (1 in the placebo group, 1 in the suanzaorentang group) and unknown reasons (1 in the placebo group, 1 in the diazepam group, 1 in the suanzaorentang group). The characteristics of the subjects who completed the study are shown in Table 1. Overall, the background characteristics of the 3 groups are comparable.

Table 2 shows the number of capsules taken over the 2nd phase for each treatment group.

Effects of suanzaorentang, diazepam and placebo on MAI, HAS and 4 HAS subset scores

As shown in Table 3, MAI and HAS scores were statistically significantly improved by diazepam

Table 3 Effects of suanzaorentang, diazepam and placebo on MAI, HAS and 4 HAS subsets scores (Mean ± SD).

Visit	1	2	3	4
MAI				
suanzaorentang	26.4 ± 7.6	25.9 ± 6.7	21.5 ± 8.9*	23.7 ± 8.5
diazepam	28.9 ± 8.2	27.7 ± 7.3	22.7 ± 8.6**	24.8 ± 8.9
placebo	27.4 ± 8.1	27.1 ± 7.5	26.8 ± 8.2	26.7 ± 8.1
HAS				
suanzaorentang	24.2 ± 5.9	23.3 ± 7.2	15.9 ± 8.2***	19.8 ± 6.7*
diazepam	23.6 ± 6.2	22.1 ± 8.1	15.5 ± 7.4***	19.6 ± 8.2*
placebo	24.5 ± 6.0	23.7 ± 7.5	23.5 ± 7.4	23.4 ± 7.3
Anxious mood				
suanzaorentang	2.1 ± 0.4	2.0 ± 0.3	1.0 ± 0.3***	1.5 ± 0.4***
diazepam	2.0 ± 0.3	1.9 ± 0.4	1.1 ± 0.4***	1.3 ± 0.3***
placebo	2.2 ± 0.5	2.1 ± 0.5	2.0 ± 0.5	2.0 ± 0.4
Cardiovascular symptoms				
suanzaorentang	2.4 ± 0.3	2.4 ± 0.4	1.0 ± 0.3***	1.7 ± 0.3***
diazepam	2.3 ± 0.4	2.3 ± 0.3	1.2 ± 0.4***	1.6 ± 0.2***
placebo	2.5 ± 0.3	2.5 ± 0.3	2.4 ± 0.3	2.3 ± 0.4
General somatic (muscular)				
suanzaorentang	2.0 ± 0.3	2.0 ± 0.4	1.6 ± 0.4***	1.9 ± 0.3***
diazepam	1.9 ± 0.3	1.8 ± 0.3	1.0 ± 0.3***	1.4 ± 0.4***
placebo	2.1 ± 0.3	2.0 ± 0.4	2.0 ± 0.3	1.9 ± 0.2
Insomnia				
suanzaorentang	1.7 ± 0.3	1.6 ± 0.2	1.0 ± 0.4***	1.3 ± 0.3**+
diazepam	1.6 ± 0.3	1.5 ± 0.4	0.5 ± 0.2***+	1.0 ± 0.4***
placebo	1.6 ± 0.4	1.5 ± 0.2	1.4 ± 0.3	1.4 ± 0.3

* $p < 0.05$ (visit 3 to visit 2; visit 4 to visit 3), ** $p < 0.01$ (visit 3 to visit 2), *** $p < 0.001$ (visit 3 to visit 2; visit 4 to visit 3), + $p < 0.001$ (diazepam to suanzaorentang)

and suanzaorentang ($p < 0.01$) but not by placebo. MAI and HAS scores were not significantly different between suanzaorentang (250 mg t.i.d.) and diazepam (2 mg t.i.d.) at visit 1, 2, 3 and 4.

From 4 subset scores in HAS, also shown in Table 3, we found that the effects of suanzaorentang (250 mg t.i.d.) on anxious mood and cardiovascular symptoms (taken here as the indices of sympathetic activity) were nearly as strong as those of diazepam (2 mg t.i.d.). However, diazepam (2 mg t.i.d.) was more potent than suanzaorentang (250 mg t.i.d.) in improving insomnia and general somatic (muscular) scores ($p < 0.05$).

Effects of suanzaorentang, diazepam and placebo on DSST and "How function" scale scores

The results are in Table 4. In the suanzaorentang group, the DSST score was slightly improved after the 1st week of placebo. However, the improvement was not statistically significant. This improvement might be due to the practice effect of repeating the test after a short interval. After the 2nd week of suanzaorentang, the DSST score was statistically significantly improved ($p < 0.001$). After the final week of placebo, the DSST score significantly deteriorated ($p < 0.05$). From the trend of the DSST score changes, we could see that the DSST score was really improved by suanzaorentang, although there was a practice effect. The DSST is a test of psychomotor performance, especially of attention and the ability to concentrate. The improvement of DSST score means the improvement of psychomotor performance.

In the diazepam or placebo group, there was a general trend of slight improvement of DSST score. However, the improvement was not statistically significant and could be explained by the practice effect.

The "how function" scale score improved significantly after the 2nd week of suanzaorentang and deteriorated after the 3rd week of placebo ($p < 0.001$). This score was not improved by diazepam or placebo. This suggested that only suanzaorentang improved the subjective feeling of psychomotor improvement during the daytime.

Effects of suanzaorentang, diazepam and placebo on RFT, LFT, electrolyte balances, serum cholesterol-triglyceride-HDL-c, fasting blood sugar, serum T_4, chest P-A X-ray film and BUS routines

Suanzaorentang, diazepam and placebo had no apparent effects on these parameters.

Table 4 Effects of suanzaorentang, diazepam and placebo on DSST and "How function" scale (Mean ± SD).

Visit	1	2	3	4
DSST				
suanzaorentang	39 ± 11	42 ± 8	51 ± 9**	46 ± 12*
diazepam	40 ± 10	43 ± 7	44 ± 10	45 ± 10
placebo	39 ± 11	42 ± 9	45 ± 8	48 ± 10
"How function"				
suanzaorentang		3.3 ± 0.5	4.0 ± 0.4**	3.6 ± 0.4**
diazepam		3.5 ± 0.3	3.6 ± 0.2	3.7 ± 0.3
placebo		3.1 ± 0.4	3.2 ± 0.3	3.3 ± 0.4

* $p < 0.05$ (visit 4 to visit 3), ** $p < 0.001$ (visit 3 to visit 2; visit 4 to visit 3)

Subjective side effects of suanzaorentang, diazepam and placebo

As summarized in Table 5, in the suanzaorentang group, 2 patients complained mild somnolence and 1 patient complained fatigue, however, they were not bothered by them and they disappeared either spontaneously or after dose reduction. In the diazepam group, 3 patients complained drowsiness during the daytime, 2 patients complained fatigue and 1 patient complained dry mouth. In the placebo group, 1 patient complained drowsiness and 1 patient complained fatigue.

Discussion

The changes in HAS, MAI and DSST scores when taking diazepam in this study are essentially not different from those reported by other researchers [Bonn et al. 1971, Borland et al. 1974].

From this study, we also found that (1) suanzaorentang (250 mg t.i.d.) and diazepam (2 mg t.i.d.)

Table 5 Subjective side effects of suanzaorentang, diazepam and placebo of the 2nd week.

	suanzaorentang		diazepam		placebo	
	patient number	incidence (%)	patient number	incidence (%)	patient number	incidence (%)
Somnolence	2	6	0	0	0	0
Drowsiness	0	0	3	10	1	3
Fatigue	1	3	2	7	1	3
Dry mouth	0	0	1	3	0	0
Total	1	9	6	20	2	6

had almost the same potency in improving anxious mood (worries, anticipation of the worst, apprehension and irritability) and sympathetic symptoms (tachycardia, palpitations, chest pain, vascular throbbing, fainting feelings and missing beat), (2) diazepam (2 mg t.i.d.) was more potent than suanzaorentang (250 mg t.i.d.) in improving general somatic (muscular) tension (muscular pains, muscular stiffness, muscular twitchings, clonic jerks, grinding of teeth and unsteady voice) and insomnia and (3) suanzaorentang (250 mg t.i.d.) improved daytime psychomotor performance but diazepam (2 mg t.i.d.) did not. These findings make us reconfirm that diazepam has wider pharmacological effects on the central nervous system.

Bowman et al. [1980] suggested that the limbic system and hypothalamus might relate to the main site of emotional reactivity and the autonomic manifestations of emotion, respectively. They also observed that the action sites of diazepam could be considered as not only above two sites but also the reticular formation (as to the arousal reactions) and the spinal cord (as to the general somatic tension). As these demonstrations and our results show, suanzaorentang may act on the same sites as diazepam.

In rats, we also found that suanzaorentang could (1) prolong the period from the onset of convulsion to the time of death induced by pentylenetetrazole or picrotoxin. (2) prolong the sleep duration induced by hexobarbital, (3) enhance the hypomotility induced by α-methyl-p-tyrosine and (4) antagonize the increased locomotor activity induced by levo-dopa plus benserazide. The biochemical mechanism of suanzaorentang's anxiolytic action may be related to the monoaminergic activity in the central nervous system [Hsieh in press].

Probably, suanzaorentang is a promising anxiolytic agent deserving further extensive studies. As an anxiolytic, suanzaorentang might be better than the standard anxiolytic of diazepam.

Acknowledgements

We thank Dr. Kuo JG, Prof. Ha HC, Dr. Chow HC and Dr. Pon CT for their help with these studies. We gratefully acknowledge the grant from the National Science Council, R.O.C. (NSC 74-0412-B039-04).

REFERENCES

American Psychiatric Association 1980 Diagnostic and Statistical manual of mental disorders (DSM III). American Psychiatric Association, Washington DC p 225

Bo O, Haffner JFW, Langard O, Trujpy JH, Bordesen JE, Lunde PKM 1974 Ethanol and diazepam as causative agents in road traffic accidents. Proceedings 6th International Conference Alcohol, Drugs and Driving, Toronto, p 439

Bonn JA, Salkind MR, Linford RW 1972 A technique in the evaluation of psychotropic medication based on a patient demand schedule: A comparison of the efficacy of oxypertine, diazepam and placebo in anxiety. Curr. Ther. Res. *19:* 92

Boralnd RG, Nicholson AN 1974 Immediate effects on human performance of a 1,5-benzodiazepine compound with the 1,4-benzodiazepine, chlordiazepoxide HCI and diazepam. Br. J. Clin. Pharmacol. *2:* 215

Bowman WC, Rand MJ 1980 Tranquillizers. Blackwell Scientific Publications, Oxford, p 774

Chang TC 115 B.C. Suanzaorentang. Kin-Kue-Yao-Lueh, China, *15*

Chen HC, Hsieh MT 1985 Studies on the suanzaorentang in the treatment of anxiety. Psychopharmacology *85:* 486

Fielding S, Hoffman I 1979 Pharmacology of anti-anxiety drugs with special reference to clobazam. Br. J. Clin. Pharmacol. *7:* 7S

Hamilton M 1959 The assessment of anxiety states by rating. Br. J. Med. Psychol. *32:* 50

Hsieh MT, Chen HC, Hsu PO 1985 The effects of suanzaorentang on the central nervous system. Proceedings National Science Council, ROC

Lader MH 1979 Anxiety reduction and sedation, Psychophysiological theory. Br. J. Clin. Pharmacol. *7:* 69S

Salkind MR 1973 The construction of the Morbid Anxiety Inventory (Ph. D. Thesis). London University, London, p1

Salkind MR, Hanks GW, Silverstone JT 1979 Evaluation of the effects of clobazam on mood and psychomotor performance in clinically anxious patients in general practice. Br. J. Clin. Pharmacol. *7:* 113S

Wechsler D 1955 Manual of the Wechsler Adult Intelligence Scale. Psychological Corporation, New York, p37

Wittenborn JR, Flaherty JR, McGouh WE, Nash RJ 1979 Psychomotor changes during the initial day of benzodiazepine medication. Br. J. Clin. Pharmacol. *7:* 69S